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REVIEW ARTICLE

The current status and future of radiotherapy for spinal bone metastases

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Abstract The management of spinal bone metastases is complex. In this review, the efficacy, methodology, and utilization of radiotherapy (RT) for spinal bone metastases are discussed. A number of randomized trials have evaluated the efficacy of 8 Gy, single-fraction RT for the palliation of painful bone metastases. However, RT for metastatic spinal cord compression has not been evaluated with respect to its optimal dose, palliative potential, or its ability to improve motor function. Two highly sophisticated RT techniques — stereotactic body RT (SBRT) and intensity-modulated RT (IMRT) — have recently been adapted for the treatment of spinal bone metastases, and both have the potential to achieve excellent control while minimizing acute and late toxicity. SBRT and IMRT are particularly well suited for the treatment of spinal bone metastases when they are localized or require re-irradiation, and may provide superior tumor control. Predicting the prognosis of patients with bone metastases and assessing spinal instability are both important when selecting the optimal RT method and deciding whether to perform surgery. The proper care of spinal bone metastases patients requires an interdisciplinary treatment approach.

Introduction

Bone metastases are a common manifestation of malignancy that can cause severe and debilitating effects, including pain, spinal cord compression, hypercalcemia, and pathologic fractures. The proper care of patients with bone metastasis requires interdisciplinary treatment delivered by orthopedic surgeons, radiation oncologists, medical oncologists, pain medicine specialists, radiologists, and palliative care professionals. Radiotherapy (RT) can provide successful palliation of painful bone metastasis in 50–80 % of patients in a time efficient manner, and is associated with very few adverse effects, allowing complete pain relief at the treated site in up to one-third of patients [1]. Recently, in the field of radiation oncology, emerging novel techniques have been developed and adapted for the treatment of bone metastases. In light of these advances, the focus of this review includes the efficacy of RT, new RT methods, and relevant prognostic factors. The significance of each of these in the management of spinal bone metastases is discussed.

Radiation dose and schedule

RT is commonly used to provide pain relief in cases of painful bone metastases. Chow et al. [2] conducted a meta-analysis of 25 randomized palliative RT trials for uncomplicated painful bone metastases comparing 8 Gy in single and 20–30 Gy in multiple fractions. They concluded that both the overall pain relief rate (60 % in the single-fraction arm and 61 % in the multiple-fraction arm) and the complete pain relief rate (23 and 24 %, respectively) were similar with no significant difference between these schedules. Although retreatment rates were higher in those who received single-fraction therapy, 8 Gy in single-fraction RT was suggested as the standard of care for the palliation of uncomplicated painful bone metastases in the recent American Society for Therapeutic Radiology and Oncology guidelines [3].

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It is possible that patients with metastatic spinal cord compression (MSCC) will benefit more from higher-dose multiple-fraction RT than they would from lower-dose single-fraction RT, although currently, there is little data to support this (Table 1). In their review, Chow et al. [1] found that spinal cord compression occurred in 5.7 and 4.1 % of patients who received single-fraction and multiple-fraction RT, respectively. Although there was a trend favoring multiple-fraction RT, this did not reach statistical significance ($P = 0.31$). Rades et al. [4] evaluated the local control achieved using different RT schedules for MSCC. In their prospective, non-randomized study, local control was found to be significantly better after a long course of treatment (30 Gy in 10 fractions, 37.5 Gy in 15 fractions, and 40 Gy in 20 fractions) compared to a shorter course (8 Gy in a single-fraction, and 20 Gy in 4 fractions). In contrast, Maranzano et al. [5] demonstrated that a single-fraction RT was sufficient, and resulted in only minimal toxicity for patients with a poor prognosis.

Rades et al. [6] suggested in their retrospective study that dose escalation beyond 30 Gy in 10 fractions did not improve motor function and local control of MSCC in radioresistant tumors, such as renal cell carcinoma, colorectal cancer, and malignant melanoma. However, in another report [7], dose escalation beyond 30 Gy was found to give better local control and extend overall survival in patients with breast cancer, prostate cancer, myeloma/lymphoma, and others who had a favorable prognosis. Thus, 30 Gy in 10 fractions could be regarded as the standard therapeutic dose for MSCC. Although the available evidence is limited, dose escalation beyond 30 Gy may improve local control and overall survival in patients with a favorable survival prognosis, but it may not improve functional outcome, and dose escalation to 40 Gy in 20 fractions may still be insufficient for radioresistant tumors.

IMRT and stereotactic body RT

Recently, two sophisticated RT techniques, stereotactic body RT (SBRT; including stereotactic radiosurgery and stereotactic RT) and intensity-modulated RT (IMRT) have been adapted for the treatment of spinal bone metastases. SBRT uses more beams from many more directions than conventional opposed-field RT and consequently delivers much higher doses in a hypofractionated manner (either as a single fraction or as a smaller number of fractions). IMRT makes it possible to deliver optimal radiation doses safely to an irregularly shaped target while minimizing the dose to the surrounding normal structures. In order to achieve a high standard of targeting precision, these approaches require that the exact location and shape of the tumor be determined using imaging techniques (Fig. 1). In general, the term "spinal SBRT" refers to the use of both IMRT techniques and SBRT. The most important additional benefit of spinal SBRT is the possibility of achieving excellent dose coverage of the target, while avoiding the spinal cord, which is often the major limiting factor when delivering high-dose RT (Figs. 1, 2). Multiple retrospective studies have demonstrated that SBRT could feasibly be used to treat spinal metastases, and could control target lesions with only low toxicity [8, 9]. The local control rate based on imaging and/or pain management criteria was reported to be greater than 80 %, with only rare cases of toxicity.

Table 1 Outcomes of conventional RT for MSCC

References	Study design	State of disease	Dose	Ambulatory rate before treatment (%)	Motor function improvement (%)	LC	Overall survival
Maranzano [5]	RCT	Unfavorable prognosis	8 Gy/1 Fr	64	12	NA	4 months (median)
			16 Gy/2 Fr	67	21	NA	4 months (median)
Rades [4]	Prospective non-RCT	Various	8 Gy/1 Fr, 20 Gy/4 Fr	61	37	61 % at 1 years	23 % at 1 year
			30–40 Gy/10–20 Fr	62	39	81 % at 1 years	30 % at 1 year
Rades [7]	Matched cohort	Favorable prognosis	30 Gy/10 Fr	85	40	71 % at 2 years	53 % at 2 years
			37.5 Gy/15 Fr 40 Gy/20 Fr	85	41	92 % at 2 years	68 % at 2 years
Rades [6]	Retrospective	Radio-resistant tumor	30 Gy/10 Fr	62	18	76 % at 1 year	NA
			37.5 Gy/15 Fr 40 Gy/20 Fr	63	22	80 % at 1 year	NA

RT radiotherapy, *MSCC* metastatic spinal cord compression, *LC* local control, *RCT* randomized controlled trial, *Fr* fraction, *NA* not available

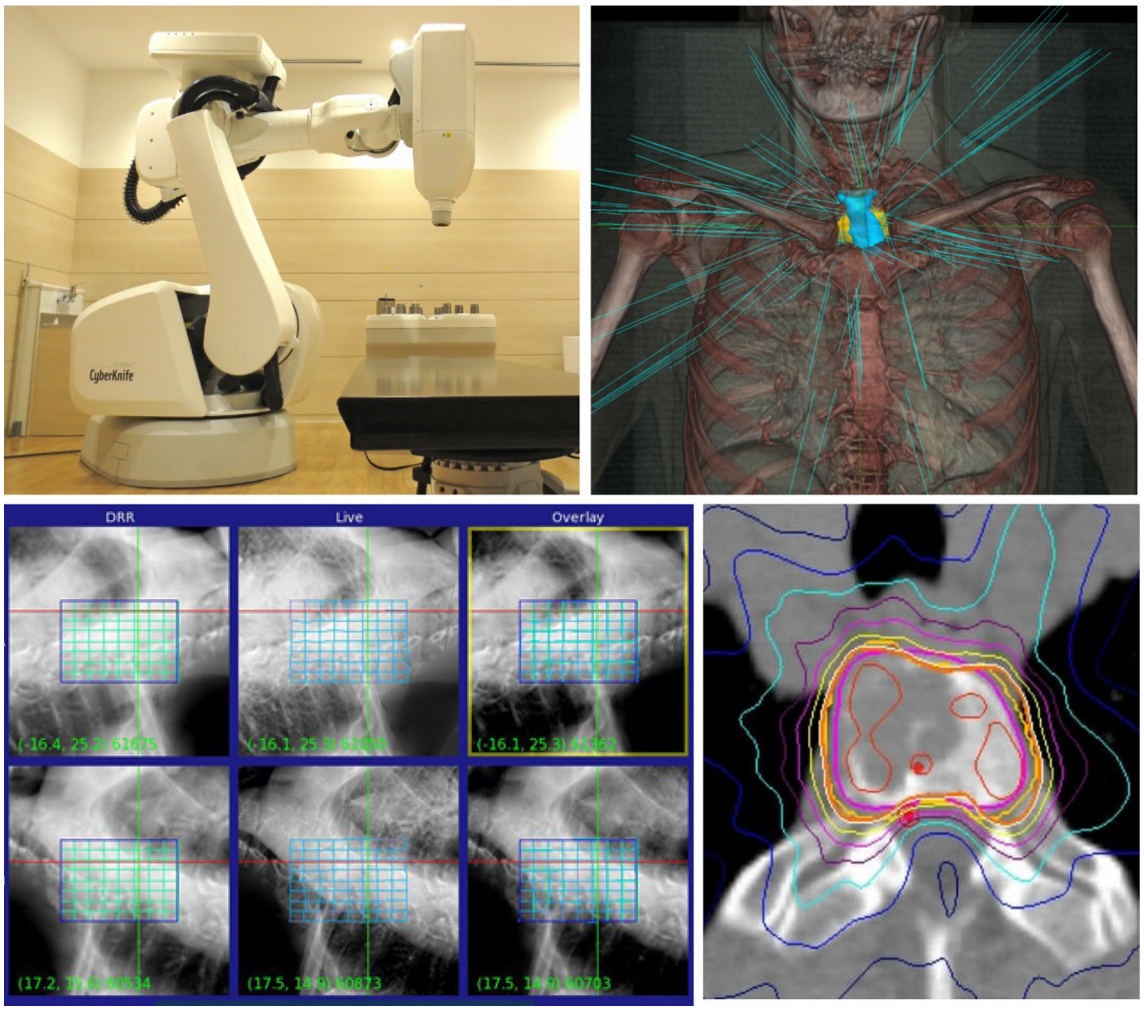

Fig. 1 *Upper panels* the CyberKnife apparatus (*left*); a 3-dimensional rendered image (*right*) *blue lines* indicate beam directions. *Lower panels* Xsight, the image-guidance system used in the CyberKnife system, enables the automatic tracking of skeletal structures (*left*). Representative dose distribution (*right*)

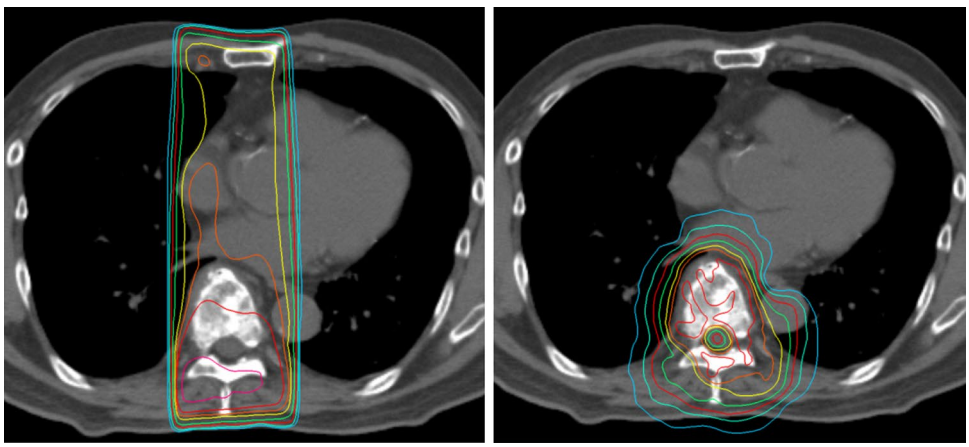

Fig. 2 Comparison of radiation dose distributions between conventional radiotherapy (*left*) and intensity-modulated radiotherapy (*right*). Each *colored line* indicates an *isodose curve*. A higher radiation dose is concentrated on the vertebral bone metastasis while avoiding the heart and lungs (*right*)

The indication and appropriateness of SBRT in the treatment of spinal bone metastases should be carefully considered. The published efficacy and safety data for SBRT have mostly been from retrospective, single institution studies. Neither the exact dosing and target delineation requirements, nor the most appropriate inclusion and exclusion criteria for SBRT have been fully defined. In most previous studies of spinal SBRT, the primary endpoint for efficacy was the local control rate based on imaging and/or pain control, while motor function and ambulatory status were rarely considered. In their guidelines for RT of bone metastasis, Lutz et al. [3] suggested that SBRT might be useful for treating spinal bone metastases, although they also advised that this should preferably be within the confines of a clinical trial.

Postoperative irradiation

Surgery plays an important role in the management of patients with symptomatic MSCC. For patients with severe MSCC, Patchell et al. [10] demonstrated that surgical decompression was beneficial in the only randomized, multi-institutional trial to date. Significantly more patients who underwent surgery plus postoperative RT regained the ability to walk compared to those who only received RT. Patients treated with surgery also retained the ability to walk significantly longer than those treated with RT alone. Moreover, surgery only restored the ability to walk in 30 % of patients who failed to respond to earlier RT, which compares unfavorably with the 62 % post-treatment ambulatory rate of the patients who were originally not able to walk and received surgery as their first treatment. Based on these findings, the authors claimed that surgery plus RT was the best first-line treatment for MSCC. However, this result conflicts with the findings of Rades et al. [11], who showed that surgery plus RT for MSCC patients with various primary tumors did not significantly improve their functional outcome compared to RT alone. They also showed that surgery was beneficial for patients with relatively radioresistant primary tumors [12] (Table 2).

Although the exact criteria for surgery in MSCC patients continue to be debated, the following are generally agreed to be necessary: a favorable survival prognosis, a good performance status, a relatively radioresistant tumor type, and MSCC accompanied with mechanical instability [13, 14]. RT alone is recommended for MSCC from highly radiosensitive tumors, such as hematological malignancies and germ cell tumors. A dose of 30 Gy in 10 fractions for MSCC in a postoperative setting is the most frequently used and is now considered to be the standard treatment [10–12]. Higher doses may also be administered to patients with a favorable prognosis. However, these doses are based

Table 2 Outcome of conventional RT with or without surgery for MSCC

References	Study design	Type of primary tumor	Surgery	Dose	Ambulatory rate before treatment (%)	Ambulatory rate after treatment (%)	Regained ability to walk (%)	LC	Overall survival
Patchell [10]	RCT	Excluded highly radiosensitive tumors	Surgery + RT	30 Gy/10 Fr	68	84	62	NA	126 days (median)
			RT	30 Gy/10 Fr	69	57	19	NA	100 days (median)
Rades [11]	Matched cohort	Various	Surgery + RT	30–40 Gy/10–20 Fr	63	69	30	90 % at 1 year	47 % at 1 year
			RT	30–40 Gy/10–20 Fr	63	68	26	91 % at 1 year	40 % at 1 year
Rades [12]	Matched cohort	Unfavorable[a]	Surgery + RT	30–40 Gy/10–20 Fr	64	67	29	85 % at 1 year	38 % at 1 year
			RT	30–40 Gy/10–20 Fr	64	61	19	89 % at 1 year	24 % at 1 year

RT radiotherapy, *MSCC* metastatic spinal cord compression, *LC* local control, *RCT* randomized controlled trial, *Fr* fraction, *NA* not available

[a] Non-small cell lung cancer, unknown primary cancer, renal cell carcinoma, and colorectal cancer

on the use of RT alone for MSCC, and there are no reports comparing optimal postoperative RT doses.

A number of retrospective reports have focused on the postoperative efficacy of SBRT in MSCC patients (Table 3). The study with the largest cohort, by Laufer et al. [16], reported that high-dose hypofractionated SBRT provided better local tumor control compared with low-dose hypofractionated SBRT. Epidural disease is one of the major factors limiting the efficacy of spinal SBRT. Al-Omair et al. [17] showed that epidural disease progression was the most common treatment failure after spinal SBRT, and postoperative epidural disease grade was a significant predictor of local control. Ideally, in order to administer a tumoricidal radiation dose by SBRT more safely, it may be possible to create a small margin of 2–3 mm between the tumor and the spinal cord by performing separation surgery. This allows a full dose to be administered to the entire tumor volume while minimizing the radiation exposure to the spinal cord. A treatment approach reported by Bate et al. [18] that included SBRT alone for patients with minimal MSCC, and separation surgery followed by SBRT for patients with high-grade MSCC, seems a reasonable strategy.

Re-irradiation of spinal bone metastases

Notably, re-irradiation is effective in improving or maintaining motor function. Rades et al. [19] conducted a retrospective study of re-irradiation for MSCC, and found that motor function improved in 36 % of patients, was stable in another 50 % of patients, and deteriorated in 14 % of patients, and that there were no cases of late toxicity, such as radiation myelopathy. The degree of motor function after re-irradiation was associated with the effectiveness of the initial RT, performance status, time to development of motor deficits, and visceral metastases, whereas the re-irradiation schedule had no significant impact. A recent multicenter, randomized trial [20] of re-irradiation for painful bone metastases, of which 28 % were in the spine, showed that treatment with 8 Gy in a single fraction was as effective as, and less toxic than 20 Gy in multiple fractions; however, these findings were not robust in per-protocol analysis.

SBRT is well suited for re-irradiation of the spine and may provide superior tumor control compared to conventional techniques, with reported local control rates of 66–93 % [21–23] (Table 4). Several studies identified potential risk factors for local recurrence after re-irradiation by spinal SBRT. Garg et al. [21] reported in their prospective study of spinal re-irradiation by SBRT that 13 of 16 patients with local progression after SBRT had tumors within 5 mm of the spinal cord, and 6 of them eventually developed MSCC. Damast et al. [22] studied the dose–response with SBRT used for re-irradiation, and found that there were significantly fewer local failures after SBRT with 30 Gy in 5 fractions compared to 20 Gy in 5 fractions.

Relatively little is known regarding the long-term toxicities of re-irradiation. Because re-irradiation has the potential to exceed normal tissue tolerance, care must be taken when the re-irradiated volume contains the spinal cord, and it might be appropriate to sum the biologically effective

Table 3 Outcomes of postoperative SBRT or SBRT alone for MSCC

References	Patients/lesions	Re-RT	Treatment	Dose	Neurological response	Postop MSCC	LC at 1 year
Ryu [15]	62/85	0	SBRT alone	12–20 Gy/1 Fr	Remained intact in 94 %, improved in 52 %, stable in 11 %, progression in 16 %	NA	NA
Laufer [16]	186	0	Surgery + SBRT		NA	11 %	83.6 %
	109	75		18–36 Gy/5–6 Fr			77.4 %
	37	14		24–30 Gy/3 Fr			95.9 %
	40	2		24 Gy/1 Fr			91 %
Al-Omair [17]	80	0	Surgery + SBRT		NA	10 %	84 %
	35	0		18–26 Gy/1–2 Fr			100 %
	45	0		18–40 Gy/3–5 Fr			70 %
Bate [18]	57/69	0				NA	94.2 %
	21 lesions	6	Surgery + SBRT	16–23 Gy/1 Fr, 20–30 Gy/3–5 Fr	Frankel score improved in 14 %, stable in 81 %, and declined in 5 %		90.5 %
	48 lesions	24	SBRT alone	16–23 Gy/1 Fr 20–30 Gy/3–5 Fr	Frankel score improved in 10 %, and stable in 90 %		95.8 %

SBRT stereotactic body radiotherapy, *MSCC* metastatic spinal cord compression, *LC* local control, *Fr* fraction, *NA* not available

Table 4 Outcomes of re-irradiation by spinal SBRT

References	Patients/lesions	Epidural disease	Dose	Neurological response	MSCC after re-RT	LC	Overall survival	No neurologic deterioration	Neural toxicity	Other toxicity
Garg [21]	59/63	None	30 Gy/5 Fr 27 Gy/3 Fr	NA	1 %	76 % at 1 year	76 % at 1 year	92 % at 1 year	2 of G3 radiculopathy	None
Mahadevan [23]	60/81	27 %	24 Gy/3 Fr 25–30 Gy/5 Fr	Radiculopathy improved 11 of 14, lower-limb weakness was stable 4 of 4	NA	93 % at last follow-up	11 months (median)	NA	3 Cases of radicular pain and 1 of lower-extremity weakness with tumor progression	None
Damast [22]	95/97	48 % Postop RT		NA	NA	66 %	13.6 months (median)	NA	None	9 VCF, 1 esophageal stricture
	42/42		20 Gy/5 Fr			55 % at 1 year				
	53/55		30 Gy/5 Fr			74 % at 1 year				

SBRT stereotactic body radiotherapy, *MSCC* metastatic spinal cord compression, *LC* local control, *Fr* fraction, *VCF* vertebral compression fracture, *NA* not available

doses (BEDs) from the initial and repeat treatment regimens in order to estimate the risk of radiation myelopathy [3]. Radiation-induced myelopathy can occur 3–25 months after RT [24, 25], although complications associated with spinal re-irradiation are only rarely reported. Higher cumulative RT doses (BED > 135.5 Gy_2), higher doses of each RT course (BED > 98 Gy_2), and a short interval between the courses (<6 months) could be associated with a higher probability of developing radiation-induced myelopathy [24].

Assessment for spinal instability in the treatment of spinal bone metastases

Spinal instability is associated with the development of neurologic deficits, mechanical pain, and progressive deformity [26]. Therefore, early recognition of impending instability may prevent painful collapse and loss of function by prompting timely referral and treatment. In order to create a simple, standardized referral tool for non-spine specialists, the Spine Oncology Study Group developed the spinal instability neoplastic score (SINS) [26], which is based on clinical and radiologic findings. Huisman et al. [27] showed that a higher SINS increased the risk of RT failure in patients with spinal metastases, independent of the performance status, primary tumor type, and symptoms. They hypothesized that metastatic spinal bone pain, predominantly caused by mechanical instability, responds less well to RT than pain that results mainly from local tumor activity.

Vertebral fracture is common after RT for metastatic spine lesions (Fig. 3). Rose et al. [28] demonstrated that lytic disease involving more than 40 % of the vertebral body and located at or below T10 confers a high risk of fracture, with correspondingly poorer clinical outcomes. Sahgal et al. [29] reported the results of the first multi-institutional study of SBRT-induced vertebral compression fractures (VCFs), including whether the SINS can predict this adverse event. The crude risk of fracture was 14 %, the median time to VCF was 2.5 months, and the majority (65 %) of VCFs occurred in the first 4 months following SBRT. Moreover, multivariable analysis identified dose per fraction (greatest risk for ≥20 Gy), in addition to 3 of the 6 original SINS criteria: baseline VCF, a lytic tumor, and spinal deformity, as significant predictors of VCF. In a review of SBRT-induced VCF, 11–47 % of patients who developed VCFs needed a salvage spinal reconstruction procedure, such as percutaneous cement augmentation procedures or open spinal reconstructive surgery [30]. These results may help clinicians identify high-risk patients who would benefit from prophylactic vertebro- or kyphoplasty.

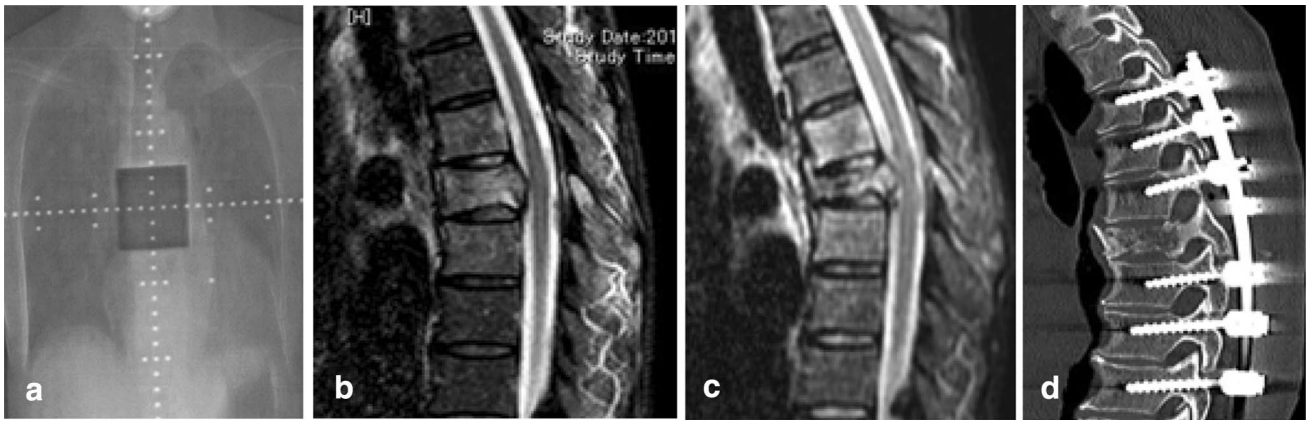

Fig. 3 Radiographs of a patient with thoracic spinal bone metastasis from breast cancer. Vertebral compression fracture deterioration at 3 months (**c**) compared to that at 1 month (**b**) after conventional radiotherapy (**a**). The patient was successfully treated via posterior stabilization (**d**)

Conclusion

RT is typically the mainstay of treatment for spinal bone metastases. A number of studies have shown that palliative RT can be effective for painful bone metastases, while relatively little is known about the management of spinal bone metastases, especially MSCC. The management of MSCC requires a consideration of motor function and spinal instability as well as pain and local control. SBRT can safely administer a higher dose to the target, and can potentially provide lasting local control. SBRT is a promising method; however, epidural recurrence after SBRT and SBRT-induced VCF continue to be problematic, and require the appropriate application of combination SBRT and surgery. An evaluation of functional outcomes following spinal SBRT and the identification of indicators for surgery are needed to establish an optimal treatment strategy for spinal metastases.

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Conflict of interest None of the authors have any conflict of interest to declare.

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